enabling safe transcutaneous photoactivation. While there are several reports in the scientific literature of utilizing the specificity of the binding between biotin and streptavidin to target tumor cells, there are no reports utilizing this ligand-receptor binding pair aimed at vascular lesions nor in conjunction with prolonged PDT light exposure (see, for example: Savitsky *et al.*, *SPIE*, 3191: 343-353,1997; and Ruebner *et al.*, *SPIE*, 2625: 328-332, 1996). In a non-PDT modality, the biotin-streptavidin-receptor binding pair has also been used as tumor targeting conjugates with radionuclides (see: U.S. Pat. No. 5,630,996 (Reno *et al.*) and with monoclonal antibodies (see: Casalini *et al*; *J. Nuclear Med.*, 38(9): 1378-1381, 1997) and U.S. Pat. No. 5,482,698 (Griffiths)).

Please replace the paragraph on page 7, line 20, through page 8, line 3, with the following paragraph:

A still further embodiment of this invention is drawn to a method for transcutaneous photodynamic therapy of target lesion in a mammalian subject comprising: administering to the subject a therapeutically effective amount of a first conjugate comprising a first member of a ligand-receptor binding pair conjugated to an antibody or antibody fragment, where the antibody or antibody fragment selectively binds to a target antigen found on thick or thin neointimas, arterial plaques, vascular smooth muscle cells and/or the abnormal extracellular matrix of the site to be treated. This step is followed by administering to the subject a therapeutically effective amount of a second conjugate comprising a second member of the ligand-receptor binding pair conjugated to a photosensitizing agent or photosensitizing agent delivery system or prodrug, where the first member binds to the second member of the ligand-receptor binding pair. A subsequent step includes irradiating at least a portion of the subject with light at a wavelength or waveband absorbed by the photosensitizing agent or if prodrug, by the product thereof. This embodiment further includes that the light is provided by a light source and that the irradiation is at a relatively low fluence rate that results in the activation of the photosensitizing agent or prodrug product.

Please replace the paragraph on page 8, lines 16-28, with the following paragraph:

Yet another embodiment of the present invention is drawn to a method for transcutaneous ultrasonic therapy of a target lesion in a mammalian subject comprising:

administering to the subject a therapeutically effective amount of an ultrasonic sensitizing agent or a ultrasonic sensitizing agent delivery system or a prodrug, where the ultrasonic sensitizing agent or ultrasonic sensitizing agent delivery system or prodrug selectively binds to the thick or thin neointimas, arterial plaques, vascular smooth muscle cells and/or the abnormal extracellular matrix of the site to be treated. This step is followed by irradiating at least a portion of the subject with ultrasonic energy at a frequency that activates the ultrasonic sensitizing agent or if a prodrug, by a prodrug product thereof, where the ultrasonic energy is provided by an ultrasonic energy emitting source. This embodiment further provides that the ultrasonic therapy drug is cleared from non-target tissues of the subject prior to irradiation.

Please replace the paragraph on page 9, lines 13-19, with the following paragraph:

Other embodiments of the present invention are drawn to the presently disclosed methods of transcutaneous PDT, where the light source is positioned in proximity to the target tissue of the subject and is selected from the group consisting of: an LED light source; an electroluminescent light source; an incandescent light source; a cold cathode fluorescent light source; organic polymer light source; and inorganic light source. A preferred embodiment includes the use of an LED light source.

Please replace the paragraph on page 11, line 25, through page 12, line 1, with the following paragraph:

Further, as used herein "target cells" or "target tissues" are those cells or tissues, respectively that are intended to be impaired or destroyed by this treatment method. Target cells or target tissues take up the photosensitizing

agent; then when sufficient radiation is applied, these cells or tissues are impaired or destroyed. Target cells are those cells in target tissues, which include, but are not limited to: vascular lesions, thick or thin neointimas, arterial plaques, neoplasms, vascular smooth muscle cells and the abnormal extracellular matrix of the site to be treated. "Non-target cells" are all the cells of an intact animal which are not intended to be impaired or destroyed by the treatment method. These non-target cells include but are not limited to healthy blood cells, and other normal tissue, not otherwise identified to be targeted.

Please replace the paragraph on page 12, lines 23-28, with the following paragraph:

"Radiation" as used herein includes all wavelengths. Preferably, the radiation wavelength is selected to match the wavelength(s) which excites the photosensitive compound. Even more preferably, the radiation wavelength matches the excitation wavelength of the photosensitive compound and has low absorption by the non-target cells and the rest of the intact animal, including blood proteins. For example, the preferred wavelength for ICG is the range of 750-850 nm.

Please replace the paragraph on page 13, line 29, through page 14, line 3, with the following paragraph:

The photosensitizing agent also can be conjugated to specific ligands reactive with a target, such as receptor-specific ligands or immunoglobulins or immunospecific portions of immunoglogulins, permitting them to be more concentrated in a desired target cell or microorganism. The photosensitizing agent may be further conjugated to a ligand-receptor binding pair, which includes, but is not limited to: biotin-streptavidin; and antigen-antibody. This conjugation may permit lowering of the required dose level since the material is more selectively targeted and less is wasted in distribution into other tissues whose destruction must be avoided.

Please replace the paragraph on page 14, line 20, through page 15, line 5, with the following paragraph:

This method comprises irradiating at least a portion of the subject with light at wavelength or waveband absorbed by said photosensitizing agent that under conditions of activation during photodynamic therapy using a relatively low fluence rate, but also at an overall high total fluence dose resulting in minimal collateral tissue damage. It is contemplated that the optimal total fluence will be determined clinically using a light dose escalation trial. It is further contemplated that the total fluence will preferably be in the range of 30 Joules to 25,000 Joules, and more preferably be in the range from 100 Joules to 20,000 Joules, and most preferably be in the range from 500 Joules to 10,000 Joules. The methods comprise irradiating at least a portion of the subject with light at a wavelength or waveband absorbed by said photosensitizing agent that under conditions of activation during photodynamic therapy using a relatively low fluence rate, but an overall high total fluence dose resulting in minimal collateral normal tissue damage. What is meant by "relatively low fluence rate" is a fluence rate that is lower than that typically used and one that generally does not result in significant damage to collateral or non-target tissues. Specifically, the intensity of radiation used to treat the target cell or target tissue is preferably between about 5 and 100 mW/cm^2. More preferably, the intensity of radiation is between about 10 and 75 mW/cm^2. Most preferably, the intensity of radiation is between about 15 and 50 mW/cm^2.

Please replace the paragraph on page 16, line 28, through page 17, line 12, with the following paragraph:

The ordinary skilled artisan would be familiar with various ligand-receptor binding pairs, including those known and those currently yet to be discovered. Those known, include, but are not limited to the group consisting of: biotin-streptavidin; and antigen-antibody. This invention contemplates a preferred embodiment that includes the use of biotin-streptavidin as the ligand-receptor binding pair. However, the ordinary skilled artisan would readily understand from the present disclosure that any ligand-receptor binding pair may be useful provided the ligand-receptor binding pair demonstrate a specificity for the

binding by the ligand to the receptor and further provided that the ligand-receptor binding pair permit the creation of a first conjugate comprising a first member of the ligand-receptor binding pair conjugated to an antibody or antibody fragment, wherein said antibody or antibody fragment selectively binds to a target antigen of thick or thin neointimas, arterial plaques, vascular smooth muscle cells and/or the abnormal extracellular matrix of the site to be treated; and further permit the creation of a second conjugate comprising a second member of the ligand-receptor binding pair conjugated to an energy sensitizing or photosensitizing agent or energy sensitizing or photosensitizing agent delivery system or prodrug, and further wherein the first member binds to the second member of the ligand-receptor binding pair.

Please replace the paragraphs on page 19, line 24, through page 20, line 4, with the following paragraphs:

C. The PDT light source is an externally positioned light source directed at the site to be treated. The light source may be a laser diode (2), light emitting diode or other electroluminescent device. The light source is angled and the light beam is focused so as to direct the light through the skin (3) or membrane of the mammalian subject being treated in a direction lengthwise and parallel to the vessel wall (5) to plaque (4). See Figures 1A and 1B.

Alternatively, the light source could comprise a laser diode (2) coupled to an optical fiber (6) which is then aimed at the vessel so as to direct the light along the length of the vessel. See Figure 2. The light source could also comprise a strip of light emitting diodes (LEDs) (7) which are then arrayed on the skin or the membrane overlying the site to be treated in the mammalian subject. See Figure 3. The light source could also comprise an optical fiber diffuser (8) which is placed over the skin or the membrane overlying the site to be treated in the mammalian subject. See Figure 4. A mirrored surface (9) may direct light downward.